Attorney's Docket No.: 06275-188001 / D 1576-1P US

#19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Tommy Ekstrom
Serial No. : 09/367,950
Filed : August 18, 1999
Title : NEW USE

Art Unit : 1617
Examiner : Jennifer Kim



Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF CHRISTER HULTQUIST, M.D.

I, Christer Hultquist, M.D., declare as follows:

1. I am a physician with a Specialty in Pediatrics (1981) and in Pediatric Allergology (1982). From 1981 to 1991 I was Senior Registrar at the Pediatric unit at the University Hospital in Lund, Sweden, attending children with cystic fibrosis, asthma and related allergic disorders. Since 1991 I have been a Medical Advisor at Astra AB (now AstraZeneca AB), and at present I am serving as the Clinical Development Medical Director for Symbicort® asthma medication (an inhalable medication containing a combination of budesonide and formoterol) at AstraZeneca AB. A copy of my *curriculum vitae* is attached.

2. Asthma is a chronic inflammatory disease of the airways. In July 1997, the National Institute of Health (NIH) published an Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (NIH Publication No 97-4051, "The NIH Guidelines"). The NIH Guidelines clearly describe what was known about asthma and asthma treatment at the time. They emphasize that persistent asthma requires both (a) long-term daily therapy to decrease the frequency and severity of asthma symptoms, and (b) appropriate medications to manage asthma episodic attacks.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

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3. Acute attacks are defined as medical emergencies and should be regarded as a failure in the long-term management of the disease. The severity of an attack of acute asthma (exacerbations of asthma in the home, in the emergency room, and in the hospital) is often underestimated by patients, their relatives and their doctors, largely because of failure to make objective measurements. If not recognized or not treated appropriately, such attacks can be fatal (M. Woodhead in "Guidelines on the management of asthma," Thorax 48 (1993), supplement S1-S24). Acute attacks demand immediate medical treatment with a medicament having fast onset of action, to rapidly alleviate the attack.

4. The NIH Guidelines categorized asthma medications into two general classes:

(1) long-term-control medications, which are taken daily on a long-term basis to achieve and maintain control of persistent asthma (also known as long-term preventive, controller, or maintenance medications), and

(2) quick relief medications, which are taken during acute attacks and at other times when prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction is needed (also known as reliever, rescue, or acute rescue medications).

5. Quick relief medications are prescribed for inhalation when the patient experiences, or expects to experience, an acute attack. These medicines provide short-term bronchodilation. They do not reduce airway inflammation. The dosage regimen for these medications is not fixed, but instead the patient is instructed to use the medication for symptomatic relief as needed, e.g., in the event of an acute attack. Prior to Applicant's invention, short-acting bronchodilators, for example, the short-acting $\beta_2$-agonists salbutamol (albuterol) and terbutaline, were the only products recommended for use on an "as needed" or "on demand" basis.

6. Long-term-control medications for maintenance treatment are prescribed for inhalation on a regular basis, typically one or more times each day, with a fixed number of doses being inhaled at each use. For example, U.S. Patent No. 5,674,860 (Carling) discloses administering budesonide/formoterol at a recommended dose regimen of twice daily (col. 3, line

43). These medicines are used to gradually reduce bronchial inflammation and thereby reduce the frequency and severity of asthma symptoms. Long-term-control medications are typically steroids.

As discussed in Carling, the dosage regimen for a maintenance medication may differ from patient to patient (col. 3, lines 44-49), depending on factors such as body weight and the physician's diagnosis of the severity of the patient's asthma. However, *for a particular patient the dosage regimen remains fixed*, i.e., the amount the patient is to inhale daily remains the same from day to day. The patient is instructed not to vary the dosage regimen without first consulting the patient's physician. If the patient experiences a change in symptoms, e.g., increased symptoms, or more frequent or more severe acute attacks, the patient must arrange an appointment with his or her physician to discuss a change in the dosage regimen. Before a drug is registered, e.g., by the FDA, it is carefully investigated for safety, and as a result of these investigations the drug is labeled to indicate how the drug should be prescribed and used. It is the responsibility of the physician to prescribe a safe dose regimen that is in accordance with the labeling and to instruct the patient to follow this regimen. Physicians do not instruct patients to take a medication "on demand" unless the medication is approved and labeled for such use, due to safety concerns, e.g., concerns with side effects, build-up of the drug in the body, and interactions with other drugs.

7. Because it is often inconvenient for the patient to consult with his or her physician, patients may tend to put off doing so. The physician cannot know that the patient's symptoms are not being properly controlled unless the patient tells the physician, and thus, absent this communication, the physician cannot remedy any problems with the patient's maintenance treatment. As a result, due to a reluctance or inability to visit the physician, the patient may continue to receive an inadequate dose of inhaled steroid.

8. Inadequate maintenance treatment, due to the patient not inhaling a sufficient dosage of inhaled steroids, may result in an acute attack. During an acute attack, the patient usually takes a short-acting $\beta_2$-agonist as a quick relief medication, as discussed above. Such a medication does nothing to treat airway inflammation or prevent future exacerbations.

9. According to the present invention, a patient is instructed to take the claimed formoterol/budesonide combination "on demand," when the patient needs symptomatic relief, for example, when the patient is or has recently been experiencing an increase in asthma symptoms. When the combination is inhaled, the patient simultaneously inhales both types of medications (budesonide for long-term-control and formoterol for quick relief). Thus, each time the formoterol/budesonide combination is inhaled by the patient, the patient obtains an extra dose of steroid. In this manner, the patient simultaneously receives both immediate relief of bronchial obstruction and anti-inflammatory treatment. The anti-inflammatory treatment is thus both immediate, providing a rapid decrease in airway obstruction, *and preventive*, providing a long-term decrease in airway inflammation. This long-term decrease in airway inflammation will tend to prevent future asthma exacerbations, which in turn will tend to reduce the overall level of asthma medication needed by the patient.

10. Recent research supports the viability of Applicant's claimed method of asthma treatment. For instance, a dose-response relationship has been shown for both budesonide and formoterol within the approved dose-range of the monoproducts (Ind et al., European Respiratory Society Annual Congress (ERS) Stockholm, September 14-18, 2002; poster P2450 (Appendix 2) and Rosenhall et al., (ERS), Stockholm, 2002, poster P388 (Appendix 3)).

Moreover, Ankerst et al. have recently shown that a combination of budesonide/formoterol in a single inhaler is well tolerated at high doses (manuscript accepted to be published in Pulm. Pharm. Ther., submitted herewith as Appendix 7). In this study, patients inhaled 12 inhalations of budesonide/formoterol at a rate of 160 μg budesonite/4.5 μg formoterol per inhaled dose, for a total daily dose of 1920 μg /54 μg. This dosage was intended to approximate the high end of the amount that might be inhaled by a patient using budesonide/formoterol on an "on demand" basis.

11. It has been shown that asthma symptoms and concomitant use of rescue (quick relief) medication consistently increase several days before the onset of a clinical exacerbation (acute attack). (Am. J. Respir. Crit. Care Med. 160(2) (1999), 594-9.) When a formoterol/budesonide

combination is prescribed for use on an "on demand" basis, as claimed, the patient will tend to use the combination more frequently in the period preceding a possible acute attack. This patient-initiated early increase in steroid dose will generally reduce the likelihood of the patient's asthma worsening, and tend to also reduce the likelihood of an acute attack that could require use of oral steroids or emergency treatment. Because the patient is instructed to use the combination on an "on demand" basis, in response to the patient's symptoms, the delay in increasing the dosage of steroid that is often caused by a patient's reluctance to consult a doctor and by time spent in obtaining an appointment can be avoided. When symptoms subside, the patient will naturally reduce the number of inhaled doses, and thus will not continue to receive an elevated dosage of steroid.

12. Because the patient can vary the number of inhaled doses based on the patient's perception of his or her asthma symptoms, the overall amount of medication that the patient inhales over the course of a month or more may actually be less than would be required if the patient's maintenance therapy were simply adjusted up and left at the higher dosage. For example, a low maintenance dose and a temporary increase in dose for 1 or 2 weeks may have the potential to control asthma as effectively as a higher maintenance dose, resulting in a lower overall daily inhaled steroid dose. Moreover, a patient using the claimed treatment protocol may suffer from fewer acute attacks, and thus may require less frequent emergency care and other acute therapy such as oral steroids. Thus, prescribing the formoterol/budesonide combination for use on an "on demand" basis may decrease the cost of health-care utilization.

Recent data support this theory. In a recently published study, patients using a formoterol/budesonide combination for maintenance therapy were instructed to increase their dose for up to 2 weeks when they found they were experiencing frequent exacerbations and/or night-time awakening due to nocturnal asthma, and then to decrease their dose when asthma control was regained. These patients maintained a health-related quality of life equivalent to that of patients receiving fixed dosing at a significantly higher overall dose (Haughney et al., ERS, Stockholm, 2002, poster P379 (Appendix 4) and Price et al., ERS, Stockholm, 2002, poster P2452 (Appendix 5).

Further, in another study, patients using the claimed "on demand" treatment protocol suffered from fewer acute attacks than a control group on a fixed dose, and thus required less frequent emergency care and other acute therapy (Olsson et al., ERS, Stockholm, 2002, poster P2451 (Appendix 6). In this study, it was found that the mean total cost of asthma-related treatment per patient, over the course of the study, was 349 Euros for the "on demand" group versus 445 Euros for the control group. The mean total cost of the Symbicort® medication alone was 217 Euros for the "on demand" group versus 357 Euros for the control group.

These results indicate that prescribing the formoterol/budesonide combination for use "on demand" may decrease the cost of health care while also improving the quality of life for asthma patients.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

By: Christer Hultquist

Christer Hultquist, M.D.

Date: 2002-12-04

# APPENDIX

# CURRICULUM VITAE

**Name**
Christer Hultquist

**Date of birth**
1 October 1946

**Nationality**
Swedish

**Education**
1977 fully qualified physician

**Postgraduate training**
1981 Certified. Pediatrician
1982 Certified in Pediatric Allergology

**Professional appointements**
Member of the Staff and Senior Registrar, Department of Pediatrics, University of Lund, 1981-1991.
Medical Adviser, Astra Draco AB, Lund, 1991-99.
AstraZeneca 1999-2000
- Global Product Physician, Pulmicort, 1999-2000
- Global Product Physician, Symbicort, June 2000 –Feb 2002
- Clinical Development Medical Director, Symbicort, March 2002

**Professional associations**
Swedish Pediatric Association
Swedish Pediatric Association for Allergy and Immunology
Swedish Association for Pulmonary Medicine
Swedish Association for Allergology
ERS
ATS

Lund 13 September 2002
Christer Hultquist

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Lund 13 September 2002

Christer Hultquist

P 2450

# Managed adjustable dosing of budesonide/formoterol combination provides equivalent asthma control to fixed dosing at a lower overall dose

Ind P[1], Haughney J[2], Price D[2], Rosen J-P[3], Kennelly J[3]

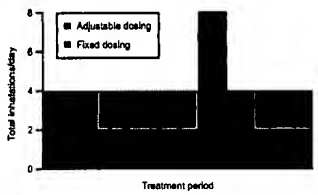
[1]Hammersmith Hospital, UK; [2]University of Aberdeen, UK; [3]AstraZeneca UK, Luton, UK

## Background

Asthma is a condition characterised by variability in airflow obstruction, fluctuation of symptoms, and changes in the level of bronchial responsiveness and airway inflammation. Recommendations from guidelines suggest the use of a long-acting $\beta_2$-agonist (LABA) in combination with an inhaled corticosteroid (ICS) in patients not controlled with ICS alone.[1] These guidelines has recently been updated to include a more flexible approach to asthma management, and advocate the use of guided self-management plans (SMPs) for patients.

Budesonide and formoterol can be conveniently administered via a single inhaler (Symbicort® Turbuhaler®). Symbicort has a fast onset of action,[2] and is well tolerated and cost effective.[3] The doses of budesonide and formoterol in Symbicort® both fall within the dose-response curve,[4,5] thus permitting adjustment of the dose by changing the number of inhalations with the same single inhaler (Figure 1). This poster focuses on the efficacy results of a study comparing fixed and adjustable dosing with Symbicort in a large number of patients with asthma in a simple SMP. Safety,[6] health economics,[7] and quality of life[8] results are reported elsewhere at this meeting.

**Figure 1.** Adjustable and fixed dosing with LABA and ICS




## Aim

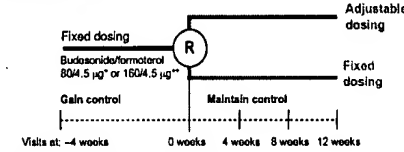
- To compare the efficacy of guided self-management using adjustable dosing of Symbicort by Turbuhaler with a fixed dose of Symbicort by Turbuhaler.

## Methods

### Study design

- Multicentre (365 centres), randomised, open study with parallel groups (Figure 2).

**Figure 2.** Study design




*Patients previously on budesonide 400–<800 µg day
**Patients previously on budesonide 800–1600 µg day

- All patients received 2 inhalations bid for 4 weeks to gain control. Of the 1734 patients enrolled, 1553 were randomised to either adjustable dosing with Symbicort (n=782), or fixed dosing with Symbicort at 2 inhalations bid for 12 weeks to maintain control (n=771).
- As-needed terbutaline by Turbuhaler (0.5 mg) was used for symptom relief.

**Table 1.** Adjustable dosing

| | Adjustment (inhalations bid) | Criteria |
|---|---|---|
| Step down | 4 to 2 or 2 to 1 | Patient unaware of recent deterioration |
| | | No night-time awakening due to asthma |
| | | SABA usage ≤2 days in previous week |
| Step up | To 4* | SABA usage ≥3 times during day |
| | | Night-time awakening due to asthma on 2 consecutive days |

*Patients continued on 4 inhalations bid for up to 14 days when treatment was reviewed
SABA: short-acting $\beta_2$-agonist

### Patients

- Male or female (≥18 years) with a history of asthma (≥6 months) on ≥400 µg/day ICS for (≥4 weeks) either;
  - stable on ICS and LABA (symptoms ≤2 days/week, short-acting $\beta_2$-agonist (SABA) ≤4/week, nocturnal disturbance ≤2 nights in previous month),

  or
  - eligible for ICS and LABA (unstable on ICS and SABA: symptoms >2 days/week, SABA >4/week, nocturnal disturbance >2 nights in previous month, $FEV_1$ or PEF <80% predicted normal).

### Primary efficacy assessments

- Treatment failure, defined as one or more of the following:
  - serious asthma exacerbation leading to use of non-study medication; hospitalisation; emergency treatment (e.g. nebulised $\beta_2$-agonist, glucocorticosteroid injection); need for a course of oral corticosteroids lasting ≥5 days; lack of efficacy requiring a change in asthma medication and withdrawal from the study.
- Treatment success, defined as improvement in symptom control according to National Institutes for Health (NIH)[1] definitions (Table 2).

**Table 2.** Definition of symptom control

| | Mild intermittent | Mild persistent | Moderate persistent | Severe persistent |
|---|---|---|---|---|
| Daytime symptoms | ≤2/week | >2/week, <1/day | Daily | Continual |
| Exacerbations | Brief | May affect activity/sleep | Affect activity/sleep ≥2/week | Frequent |
| Nocturnal symptoms | ≤2/month | >2/month | >1/week | Frequent |
| FEV, % predicted or PEF | ≥80% | ≥80% | 60–80% | ≤60% |
| PEF variability | <20% | 20–30% | >30% | >30% |
| Others | | | Daily SABA use | Limited physical activity |

Patient allocated to most severe category for which he/she met ≥1 criterion

### Secondary efficacy assessments

- Secondary efficacy variables included PEF, asthma-free days (no SABA, no nocturnal awakenings), night-time awakenings, use of SABA (inhalations/day), and number of study drug inhalations (all derived from diary card data).

### Statistical analyses

- Primary efficacy variables were compared using the Cochran Mantel-Haenszel test. Secondary efficacy variables were analysed using descriptive statistics and 95% confidence intervals of the adjusted difference, based on an ANCOVA model.

## Results

### Patients

**Table 3.** Demographic and baseline characteristics

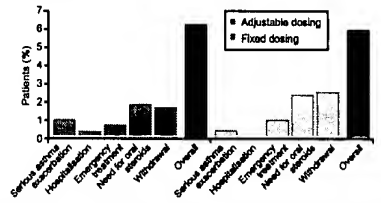
| | Adjustable dosing | Fixed dosing |
|---|---|---|
| n (male/female) | 782 (299/483) | 771 (315/456) |
| Mean age (y) | 48.7 | 48.0 |
| Mean clinic PEF (l/min)* | 416 | 423 |
| Symptom control (%)* | | |
| Severe persistent | 31 (4%) | 27 (4%) |
| Moderate persistent | 260 (34%) | 253 (33%) |
| Mild persistent | 249 (32%) | 233 (30%) |
| Mild intermittent | 235 (30%) | 251 (33%) |
| Mean pre-study steroid dose (µg) | 674 | 670 |
| Quality of life* | | |
| Mean MiniAQLQ overall score ± SD | 4.6 ± 1.2 | 4.6 ± 1.2 |

*All patients who received ≥1 dose of study medication during weeks 0 to 12; adjustable dosing n=775, fixed dosing n=764

### Efficacy

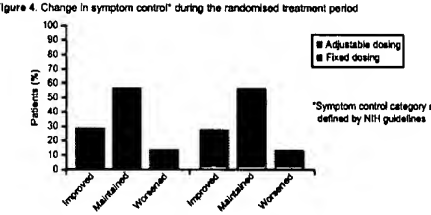
- Control of asthma was gained in both groups during the first 4 weeks, when all patients received fixed dosing; symptom control was maintained in 60% and improved in 31% of patients.

**Figure 3.** Treatment failures




- Throughout the randomised treatment period, the percentage of patients in both groups with treatment failure was low (Figure 3).
- In the same period, symptom control was improved or maintained in 86% of patients receiving adjustable dosing compared with 85% of patients receiving fixed dosing (Figure 4). There were no clinically significant differences between groups in PEF, number of asthma-free days and night-time awakenings.

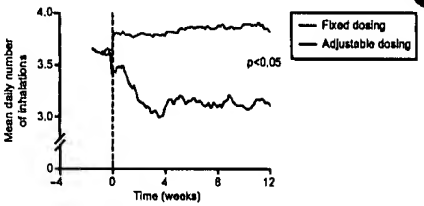
**Figure 4.** Change in symptom control* during the randomised treatment period




*Symptom control category as defined by NIH guidelines

- The mean number of daily inhalations was lower (Figure 5) in the adjustable dosing group than in the fixed dosing group (3.2 versus 3.8; $p<0.05$).

**Figure 5.** Mean daily dose of Symbicort® (inhalations)




- Reliever medication use was significantly lower in the adjustable dosing group compared with the fixed dose group (1.1 inhalations/day versus 1.2; $p<0.05$).
- Patients were able to use the plan effectively:
  - 79% of patients stepped down to 1 inhalation of Symbicort Turbuhaler bid on at least 1 day of the study; 69% stepped down for at least 1 week.
  - of those patients who stepped down, 20% stepped up at least once during the study in response to variability in the severity of symptoms.

## Conclusions

- Symbicort® by Turbuhaler® effectively gains and then maintains control of asthma with few patients experiencing exacerbations.
- Adjustable dosing with Symbicort® by Turbuhaler® is practical in a large group of patients with asthma and is at least as effective as a fixed-dose regimen in reducing symptom severity and maintaining disease control.
- Adjustable dosing results in a significantly lower overall dose of Symbicort® compared with a fixed-dose regimen.
- Symbicort® Turbuhaler® simplifies the treatment of asthma while retaining the ability to adjust maintenance therapy according to the level of symptoms, consistent with current asthma treatment guidelines.

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AstraZeneca

App. 2

P388

# Efficacy, safety and cost of budesonide/formoterol in a single inhaler compared with budesonide plus formoterol as separate inhalers

Rosenhall L[1], Elvstrand A[2], Tilling B[3], Vinge I[4], Jemsby P[5], Ståhl E[6], Jerre F[6], Ericsson K[6], Borg S[6], Callréus T[6], Bergqvist PBF[6]

[1]Huddinge Hospital, Stockholm, Sweden; [2]Vårdcentralen Kil, Kil, Sweden; [3]Vårdcentralen, Åtvidaberg, Sweden; [4]Fysikalisk Medicin, Lidingö, Sweden; [5]Sjukhuset i Varberg, Varberg, Sweden; [6]AstraZeneca R&D Lund, Lund, Sweden

## Background

Current international guidelines for the management of asthma recommend the use of an inhaled corticosteroid (ICS) in conjunction with a long-acting $\beta_2$-agonist (LABA) for those patients whose asthma is not adequately controlled by ICS alone.[1] Several studies have demonstrated that this approach is of more clinical benefit to asthma patients than increasing the dose of ICS.[2,3] Symbicort® Turbuhaler® includes the ICS budesonide and the rapid- and long-acting $\beta_2$-agonist formoterol in a single inhaler. Short-term studies have demonstrated that Symbicort is an effective and well-tolerated treatment for asthma.[4] Administration of the two drugs in a single inhaler may provide a more convenient and cost-effective treatment option than use of separate inhalers.

## Aim

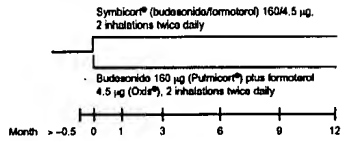
To compare the efficacy, safety and costs of treatment with Symbicort with those of budesonide and formoterol via separate inhalers over a 12-month treatment period.

## Methods

### Study design

Multicentre, open-label, randomised, parallel-group study. Randomisation was 2:1.

**Figure 1.** Study design




### Safety and efficacy assessments

- Number of withdrawals and time to withdrawal.
- Adverse events (AEs), pulse, systolic and diastolic blood pressure, electrocardiography (ECG), urinalysis, clinical chemistry, and haematology were monitored.
- Spirometry.
- Mini Asthma Quality of Life Questionnaire (MiniAQLQ), a self-administered, 15-item questionnaire covering four domains: symptoms, activity limitation, emotional function, and environmental stimuli.[5]
- Asthma Control Questionnaire (ACQ), a self-administered, 7-item questionnaire on symptoms, use of rescue medication, and $FEV_1$.[6]

### Cost assessments

*Direct costs*

- Patients recorded utilisation of the following healthcare resources:
  - all asthma-related medications (including study drugs, as-needed medications and other asthma medications)
  - hospitalisations; emergency-room visits; visits to physicians, nurses or pharmacies; phone contacts with physicians and house calls by physicians and/or nurses.
- Medication costs and official unit cost estimates were used for each resource item used. These estimates reflected the price level for 1999 expressed as SEK (1 SEK = US$ 0.10 and 0.11 Euro, May 2002).

*Indirect costs*

- Patients recorded absence from work.
- Indirect costs (the cost of days absent from work due to asthma) were estimated using the average wage of a Swedish employee in 1999.

### Statistical analysis

- All analyses were conducted on an intention to treat basis.
- Changes in $FEV_1$ from baseline and between treatments were analysed using a multiplicative analysis of variance (ANOVA).
- Changes in MiniAQLQ and ACQ from baseline and between treatments were analysed using an additive ANOVA.
- Differences in the number of withdrawals between treatments were analysed using the log-rank test.
- Patients who discontinued during the study had their mean value of actual resource utilisation extrapolated to correspond to the full 12 months (the patient-year approach).[7]
- Cost differences between groups were analysed by t-test.

## Results

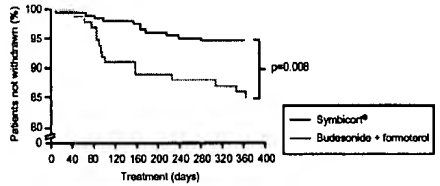
### Study patients

**Table 1.** Patient baseline characteristics

| | Treatment | |
|---|---|---|
| | Symbicort® | Budesonide plus formoterol |
| n | 218 | 103 |
| Male; n (%) | 97 (44.5) | 50 (48.5) |
| Female; n (%) | 121 (55.5) | 53 (51.5) |
| Age, y; mean (range) | 44.0 (18–78) | 43.2 (19–78) |
| Time since diagnosis of asthma, y; mean (range) | 17.9 (1–61) | 18.2 (1–63) |
| Daily dose of inhaled GCS at entry, mg; mean (range) | 694.9 (400–1600) | 671.1 (400–1200) |
| $FEV_1$, l; mean (range) | 2.93 (1.2–5.5) | 2.99 (1.5–5.0) |
| $FEV_1$, % predicted; mean (range) | 94.3 (52–139) | 95.5 (61–139) |
| Rate of employment (%) | 67.1 | 65.5 |

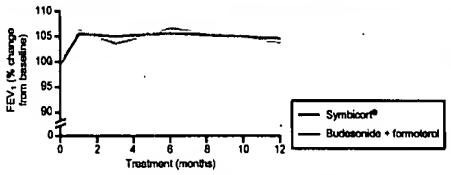
### Efficacy

**Figure 2.** Time to withdrawal



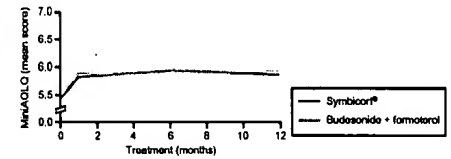

- Significantly fewer patients in the Symbicort group withdrew from the study compared with patients in the budesonide plus formoterol group (9% versus 19%, p=0.008; Figure 2).
- Reasons for withdrawal included asthma worsening, non-compliance with the protocol, and adverse events (AEs).
- Fewer discontinuations due to worsening asthma were observed in the Symbicort group compared with the budesonide plus formoterol group (1% versus 5%).

**Figure 3.** Lung function: geometric mean values (% change from baseline) of $FEV_1$



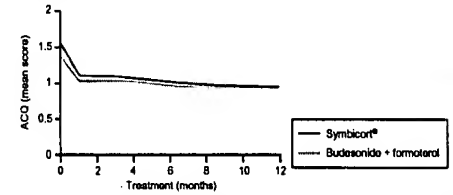

- Increases in $FEV_1$ from baseline (4–6%) were observed in both treatment groups. These improvements were already evident after 1 month of treatment and were maintained throughout the study (Figure 3).

**Figure 4.** MiniAQLQ scores




- Both treatments resulted in improvements in all four individual domain scores. Improvements in overall MiniAQLQ scores were 0.42 and 0.43 for Symbicort and separate inhalers, respectively (Figure 4).

**Figure 5.** ACQ scores




- Clinically relevant improvements in asthma control were observed in both treatment groups (Figure 5). The adjusted mean ACQ values were −0.58 for Symbicort and −0.50 for the budesonide plus formoterol group.

### Safety

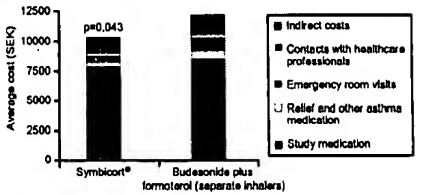
- The incidences of AEs were low and similar in both treatment groups with the majority being of mild to moderate intensity (Table 2). Respiratory infection was the most frequent AE in both groups (55% Symbicort versus 46% budesonide plus formoterol). There were no significant differences between treatment groups in the frequency of AEs.
- There were no clinically important differences between treatments regarding vital signs, ECG parameters, clinical chemistry, haematology, or urinalysis.

**Table 2.** Incidence and severity of AEs

| | Treatment | |
|---|---|---|
| | Symbicort® (n=218) | Budesonide plus formo (n=103) |
| Number of AEs/1000 treatment days | 6 | 6 |
| % total (n) of AEs | | |
| Severe | 10 (51) | 10 (19) |
| Moderate | 41 (203) | 44 (67) |
| Mild | 49 (245) | 47 (93) |

### Cost of treatment

**Figure 6.** Average costs per patient during treatment for 12 months




- Healthcare resource utilisation was low in both treatment groups and no hospitalisations were reported.
- Costs of healthcare resource use (omitting costs of study medication) were lower for Symbicort (by 687 SEK) and the difference increased with time throughout the study.
- Costs due to absence from work were numerically lower for Symbicort than budesonide plus formoterol (by 289 SEK).
- Direct, and overall treatment costs of Symbicort were significantly lower compared with budesonide plus formoterol by 1595 SEK (p=0.0004) and 1884 (p=0.043) SEK, respectively.

## Conclusions

- Symbicort® is well tolerated, is at least as effective, and is associated with significantly lower overall costs compared with treatment with equivalent doses of budesonide and formoterol via separate inhalers in the long-term treatment of asthma.
- Significantly fewer patients withdrew from treatment with Symbicort® compared with budesonide and formoterol from separate inhalers.
- Long-term adherence to treatment may be improved with Symbicort®, due to the greater simplicity and convenience of treatment with a single inhaler compared with separate inhalers.

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App. 3

P 379

# Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients

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## Background

Asthma is a variable and chronic disease that can severely restrict patients' daily life, regardless of severity.[1,2] The impact of asthma on health-related quality of life (HRQoL) is similar to other chronic diseases (SF-36 scores are similar to those in patients with arthritis and diabetes).[3] International guidelines recommend guided self-management plans (SMPs) for individuals with asthma,[4] but to date, these have only been tested in patients receiving inhaled corticosteroids (ICS) alone. With the increasing use of long-acting $\beta_2$-agonists (LABA), it is important, particularly for combination products, where it is not possible to alter the ICS dose without affecting the LABA dose, that the dose-response characteristics of these products are tested in SMPs. The doses of budesonide and formoterol in Symbicort® both fall within the dose-response curve,[5,6] thus permitting adjustment of the dose by changing the number of inhalations with the same single inhaler. This poster focuses on the effect of adjustable and fixed dosing with Symbicort on HRQoL in a comparative study; efficacy,[7,8] safety® and health economic[10] results are reported elsewhere at this meeting.

## Aim

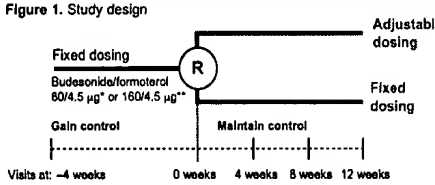
- To compare the HRQoL of patients receiving Symbicort by Turbuhaler® with adjustable dosing (dose adjusted up and down in response to asthma symptom control) or fixed dosing.

## Methods

### Study design

- Multicentre (365 centres), randomised, open study with parallel groups (Figure 1).

**Figure 1.** Study design




*Patients previously on budesonide 400–<800 µg day
**Patients previously on budesonide 800–1600 µg day

- All patients received 2 inhalations bid for 4 weeks to gain control. Of the 1734 patients enrolled, 1553 were randomised to either adjustable dosing with Symbicort (n=782), or fixed dosing with Symbicort at 2 inhalations bid for 12 weeks to maintain control (n=771).
- As-needed terbutaline by Turbuhaler (0.5 mg) was used for symptom relief.

**Table 1.** Adjustable dosing

| | Adjustment (inhalations bid) | Criteria |
|---|---|---|
| Step down | 4 to 2 or 2 to 1 | Patient unaware of recent deterioration<br>No night-time awakening due to asthma<br>SABA usage ≤2 days in previous week |
| Step up | To 4* | SABA usage ≥3 times during day<br>Night-time awakening due to asthma on 2 consecutive days |

*Patients continued on 4 inhalations bid for up to 14 days when treatment was reviewed
SABA: short-acting $\beta_2$-agonist

### Patients

- Male or female (≥18 years) with a history of asthma (≥6 months) on ≥400 µg/day ICS for (≥4 weeks) either:
  - stable on ICS and LABA (symptoms ≤2 days/week, short-acting $\beta_2$-agonist (SABA) ≤4/week, nocturnal disturbance ≤2 nights in previous month),

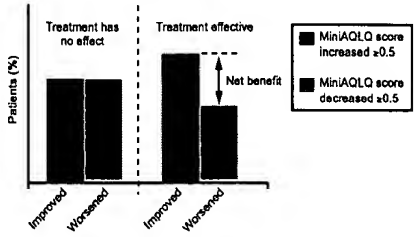
  or
  - eligible for ICS and LABA (unstable on ICS and SABA: symptoms >2 days/week, SABA >4/week, nocturnal disturbance >2 nights in previous month, $FEV_1$ or PEF <80% predicted normal).

### Assessments

- At weeks –4, 0 and 12, patients completed a self-administered Mini Asthma Quality of Life Questionnaire (MiniAQLQ).[11] An increment of 0.5 in the MiniAQLQ score is considered to be clinically relevant.
- The MiniAQLQ comprises 15 questions, each rated on a scale of 1–7, in four domains: activity, emotional, environmental, and symptoms. A higher score indicates better HRQoL. The proportion of patients experiencing a net benefit in HRQoL was calculated according to the method of Guyatt et al.[12]

*Net benefit in HRQoL = % patients with increase in MiniAQLQ score ≥0.5 – % patients with decrease in score ≥0.5 (figure 2).*

**Figure 2.** Calculation of net benefit in HRQoL




## Results

### Patients

**Table 2.** Demographic and baseline characteristics

| | Adjustable dosing | Fixed dosing |
|---|---|---|
| n (male/female) | 782 (299/483) | 771 (315/456) |
| Mean age (y) | 48.7 | 48.0 |
| Mean clinic PEF (l/min)* | 416 | 423 |
| Symptom control (%)* | | |
| Severe persistent | 31 (4%) | 27 (4%) |
| Moderate persistent | 260 (34%) | 253 (33%) |
| Mild persistent | 249 (32%) | 233 (30%) |
| Mild intermittent | 235 (30%) | 251 (33%) |
| Mean pre-study steroid dose (µg) | 674 | 670 |
| HRQoL* | | |
| Mean miniAQLQ overall score ± SD | 4.6 ± 1.2 | 4.6 ± 1.2 |

*All patients who received ≥1 dose of study medication during weeks 0 to 12; adjustable dosing n=775, fixed dosing n=764

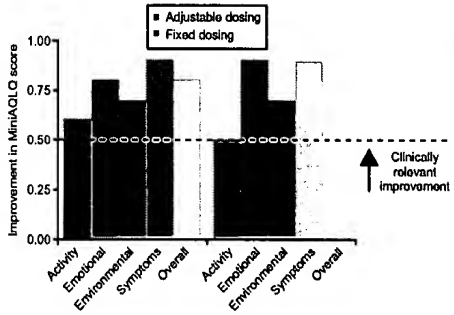
### Dosing

- Compared with fixed dosing, patients receiving adjustable dosing used statistically significantly less Symbicort (3.2 versus 3.8 inhalations/day, $p<0.05$).
- Reliever medication use was significantly lower in the adjustable dosing group than the fixed dose group (1.1 versus 1.2 inhalations/day, $p<0.05$).

### Health-related quality of life

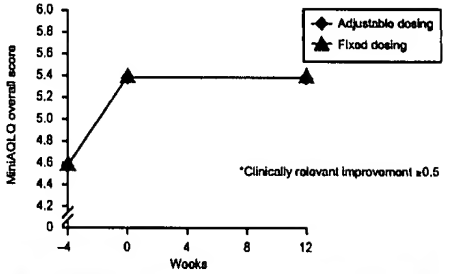
- Clinically relevant improvements in HRQoL occurred during the gain control period (improvement in MiniAQLQ scores >0.5 overall and in all domains) in both treatment groups (Figure 3).

**Figure 3.** Improvement in HRQoL during the gain control period




- More than 50% of patients in both treatment groups experienced a net benefit in HRQoL during the first 4 weeks of the study which was maintained during the randomised treatment period.
- Improvements were subsequently maintained throughout the study (Figure 4).

**Figure 4.** Symbicort® achieved and maintained clinically relevant improvements* in HRQoL: overall MiniAQLQ scores




## Conclusions

- Symbicort® rapidly improved and then effectively maintained health-related quality of life.
- Patients using Symbicort® adjustable dosing effectively stepped up and stepped down their dose according to their level of symptom control, maintaining an equivalent health-related quality of life compared with patients on fixed dosing, but at a significantly lower overall dose.

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App. 4

P 2452

# Budesonide/formoterol with an adjustable maintenance plan costs less and is as effective as fixed dosing

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[1]University of Aberdeen, Aberdeen, UK; [2]Fourth Hurdle Consulting Ltd, London, UK; [3]AstraZeneca UK, Luton, UK

## Background

Current guidelines recommend that asthma therapy be stepped up to achieve control and, when control is achieved, stepped down to maintain control with the least possible medication.[1,2] Guided self-management plans (SMPs) are an effective way for patients to monitor and adjust their medication in response to the normal variability of their symptoms.[3] Dose reduction whilst maintaining control is an obvious means towards lowering costs of asthma treatment, which are estimated to be in excess of £2000 million/year in the UK.[4] If successful, guided SMPs, may result in dose reduction, which in turn is likely to improve the cost-effectiveness of such therapy compared with standard fixed-dose regimens. The doses of budesonide and formoterol in Symbicort® both fall within the dose-response curve,[5,6] thus permitting adjustment of the dose by changing the number of inhalations with the same single inhaler. Results reported elsewhere at this meeting demonstrate that adjustable dosing with Symbicort is similarly well tolerated and equally effective as fixed dosing in maintaining asthma control but at a significantly reduced overall dose.[7–10] An economic analysis of this study, from a UK perspective, is reported here.

## Aim

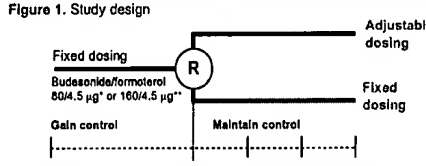
- To compare the costs and effectiveness of Symbicort adjustable dosing with fixed dosing.

## Methods

### Study design

- Multicentre (365 centres), randomised, open study with parallel groups (Figure 1).

**Figure 1.** Study design




*Patients previously on budesonide 400–<800 µg day

**Patients previously on budesonide 800–1600 µg day

- All patients received 2 inhalations bid for 4 weeks to gain control. Of the 1734 patients enrolled, 1553 were randomised to either adjustable dosing with Symbicort (n=782), or fixed dosing with Symbicort at 2 inhalations bid for 12 weeks to maintain control (n=771).
- As-needed terbutaline inhaler (0.5 mg) was used for symptom relief.

**Table 1.** Adjustable dosing

| | Adjustment (inhalations bid) | Criteria |
|---|---|---|
| Step down | 4 to 2 or 2 to 1 | Patient unaware of recent deterioration<br>No night-time awakening due to asthma<br>SABA usage ≤2 days in previous week |
| Step up | To 4* | SABA usage >3 times during day<br>Night-time awakening due to asthma on 2 consecutive days |

*Patients continued on 4 inhalations bid for up to 14 days when treatment was reviewed SABA; short-acting $\beta_2$-agonist

### Patients

- Male or female (≥18 years) with a history of asthma (≥6 months) on ≥400 µg/day inhaled corticosteroids (ICS) for (≥4 weeks) either:
  - stable on ICS and long-acting $\beta_2$-agonist (LABA),
  - or
  - requirement for LABA (unstable on ICS and short-acting $\beta_2$-agonist [SABA]).

### Effectiveness variables

- Primary: the net proportion of patients experiencing a benefit in health-related quality of life (HRQoL) as measured by the Mini Asthma Quality of Life Questionnaire (MiniAQLQ).[11,12]

  *Net benefit in HRQoL = % patients with increase in MiniAQLQ score ≥0.5 – % patients with decrease in score ≥0.5.*

- Secondary:
  - symptom-free days: no SABA use, no nocturnal awakenings
  - successfully treated days: PEF >80% of baseline, SABA <4 inhalations/day, no nocturnal awakenings.

### Statistical analysis

- A sample size of 733 patients per group was deemed necessary to detect a clinically relevant difference in treatment failure rate of 5% (11% versus 16%) with 80% power at the 5% significance level.

### Healthcare resource use and costs

- Patients recorded details of their medication use and healthcare contacts in a diary every day.
- Medication costs were calculated by multiplying the daily cost of medication by the number of days each patient was on the medication.
- Healthcare contact costs were calculated by multiplying the resource use data by unit cost data, taken from published sources at UK 2001 prices.
- 95% confidence intervals for total cost per patient per day were calculated using non-parametric bootstrapping.

## Results

### Patients

**Table 2.** Demographic and baseline characteristics

| | Adjustable dosing | Fixed dosing |
|---|---|---|
| n (male/female) | 782 (299/483) | 771 (315/456) |
| Mean age (y) | 48.7 | 48.0 |
| Mean clinic PEF (l/min)* | 416 | 423 |
| Symptom control (%)* | | |
| Severe persistent | 31 (4%) | 27 (4%) |
| Moderate persistent | 260 (34%) | 253 (33%) |
| Mild persistent | 249 (32%) | 233 (30%) |
| Mild intermittent | 235 (30%) | 251 (33%) |
| Mean pre-study steroid dose (µg) | 674 | 670 |
| HRQoL* | | |
| Mean MiniAQLQ overall score ± SD | 4.6 ± 1.2 | 4.6 ± 1.2 |

*All patients who received ≥1 dose of study medication during weeks 0 to 12; adjustable dosing n=775, fixed dosing n=764

### Effectiveness

- Clinically relevant improvements in HRQoL were seen overall and in each of the individual domains of the MiniAQLQ (increase in score ≥0.5). HRQoL scores were similar in the adjustable and fixed dosing groups.
- There were no significant differences in primary (HRQoL; Table 3) and secondary effectiveness variables (Figure 2) between adjustable and fixed dosing.

**Table 3.** Net benefits in HRQoL (primary effectiveness variable)

| | Run-in period | Randomised treatment period |
|---|---|---|
| Adjustable dosing | 53.0% | 1.2%* |
| Mean (95% CI) | (48.0 to 57.3%) | (–4.4 to 8.0%) |
| Fixed dosing | 55.6% | 5.7%* |
| Mean (95% CI) | (50.4 to 60.2%) | (0.6 to 10.3%) |

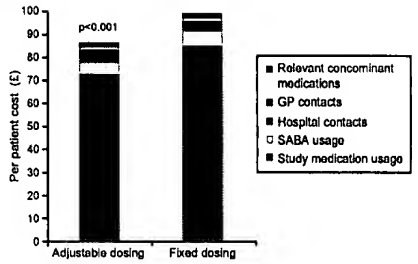
Deteriorations in HRQoL were observed in 6% (both groups) in weeks –4 to 0 and 18% (fixed) and 21% (adjustable) in weeks 0 to 12. *p=non-significant

**Figure 2.** Secondary effectiveness variables


### Healthcare resource use and costs

- As both treatments were similarly effective, no incremental cost-effectiveness ratios could be calculated.

**Figure 3.** Per patient cost of treatment




- Compared with fixed dosing, the use of Symbicort adjustable dosing resulted in a significant reduction in overall use of controller (3.2 versus 3.8 inhalations/day, p<0.05) and reliever medication (1.1 versus 1.2 inhalations/day, p<0.05). The resultant overall daily cost of treatment per patient for adjustable dosing was highly statistically significantly lower than for fixed dosing (adjustable dosing £1.13, 95% CI £1.08–1.18; fixed dosing £1.31, 95% CI £1.27–1.34; difference –0.17; 95% CI: 0.11, –0.23; p<0.001). The total cost of treatment per patient during the randomised study period is presented in figure 3.
- Switching patients from fixed to adjustable dosing was estimated to result in an annual reduction in healthcare costs of £66 per patient, which a budget analysis estimated could save the UK National Health Service £4.6 million per year (Table 4).

**Table 4.** Budget impact analysis

| Parameter | Estimated value |
|---|---|
| UK population aged over 18 years (n) | 46,222,000 |
| Adults with asthma (%) | 0.04[7] |
| Step 3 adult asthmatics (%) | 0.02[13] |
| Number of Step 3 adult asthmatics | 369,776 |
| Step 3 adult asthmatics on Symbicort (estimate; %) | 20 |
| Proportion of Step 3 adult asthmatics self-managed (%) | 8[14] |
| Population available to treat (n) | 70,032 |
| Cost per patient per year on adjustable dosing regimen (£) | 412.45 |
| Cost per patient per year on fixed-dose regimen (£) | 478.15 |
| Annual budget saving of switching (£) | 4.6 million |

## Conclusions

- **Symbicort® adjustable dosing is associated with significantly less use of controller medication, and reduced overall healthcare costs, compared with fixed dosing, while providing a similarly high degree of asthma control.**
- **Budget impact analyses demonstrate that switching patients receiving Symbicort® from fixed to adjustable dosing could result in an annual National Health Service cost saving of £4.6 million in the UK.**

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App 5

P 2451

# Adjustable maintenance treatment of asthma with budesonide and formoterol in a single inhaler

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[1]Sjöbo Primary Health-care Centre, Sweden; [2]Trosa Primary Health-care Centre, Sweden; [3]AstraZeneca Lund, Sweden

## Background

Asthma is characterised by fluctuating symptoms and periodic exacerbations.[1] Maintenance treatment therefore needs to be adjusted in response to the variable nature of the disease. Furthermore, updated guidelines recommend a more flexible approach to asthma management, and advocate the use of guided self-management plans.[2]

This study investigated a new asthma management strategy using budesonide and formoterol in the same single inhaler (Symbicort® Turbuhaler®) to effectively gain and maintain asthma control according to an adjustable treatment regimen.

## Aim

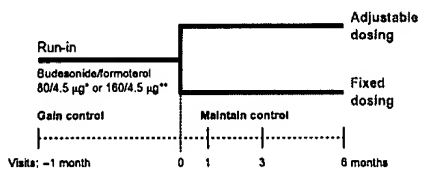
- To compare the efficacy, safety and cost of adjustable dosing with fixed dosing of Symbicort Turbuhaler in patients with asthma.

## Methods

### Study design

- Multicentre, randomised, open, parallel-group study (Figure 1).

**Figure 1.** Study design




*Patients previously on ICS 400 – ≤500 µg/day
**Patients previously on ICS >500 – ≤1000 µg/day

- After a 4-week run-in period of fixed dosing (2 inhalations bid), 1034 patients were randomised to receive a further 6 months of either fixed dosing (2 inhalations bid) or adjustable dosing (step down to 1 inhalation bid as soon as asthma control is satisfactory, increase to 4 inhalations bid for 1–2 weeks in periods of asthma worsening).
- The initial step down (judged by the investigator at a clinic visit) was taken if the patient felt well controlled, had used reliever medication ≤2 times in the last week, and had no night-time awakening due to asthma in the last week.
- Terbutaline Turbuhaler or salbutamol was available as-needed as reliever treatment.
- Patients who could not step down after 7 days of step-up treatment continued for a further 7 days and then tried to step down again using the same criteria. Patients who could not step down after 14 days contacted the investigator to decide on further treatment.

**Table 1.** Criteria for stepping up and down in the adjustable dosing arm

| | Adjustment (inhalations bid) | Criteria |
|---|---|---|
| Step up (judged by the patient) | 1 to 4 | Two consecutive days/nights with:<br>– Reliever medication used ≥3 times during day<br>OR<br>– Night-time awakening due to asthma<br>OR<br>– Morning PEF <85% mean baseline value |
| Step down after 7 or 14 days of step-up treatment (judged by the patient) | 4 to 1 | Last two consecutive days/nights with:<br>– No more asthma symptoms than before the worsening, as judged by the patient<br>AND<br>– No reliever medication used<br>AND<br>– No night-time awakening due to asthma<br>AND<br>– Morning PEF ≥85% mean baseline value |

### Patients

- Patients with asthma (according to American Thoracic Society criteria[3]) aged ≥12 years, receiving inhaled corticosteroids (ICS) for at least 6 months before enrolment at a dose of 400–1000 µg/day for 30 days before enrolment, either:
  - well-controlled on treatment with ICS and regular daily long-acting $\beta_2$-agonist (LABA), or
  - uncontrolled on ICS plus short-acting $\beta_2$-agonist.

### Primary efficacy assessments

- Exacerbation, defined as one or more of the following: asthma-related serious adverse event (SAE); treatment at a medical care unit due to worsening of asthma; use of oral corticosteroid for asthma; or study withdrawal due to need for additional asthma maintenance therapy.

### Other assessments

- Intake of study medication and overall treatment evaluation.
- Direct and indirect asthma-related costs.
- Number of SAEs and discontinuations due to adverse events (DAEs).

### Statistical analyses

- Exacerbation rate was compared between treatment groups using a Cochran Mantel-Haenszel test.
- Secondary efficacy variables and health economic variables were compared using analysis of variance.

## Results

### Patients

**Table 2.** Demographics and baseline characteristics

| | Fixed dosing | Adjustable dosing |
|---|---|---|
| n, (male/female) | 517 (214/303) | 517 (202/315) |
| Mean age, years | 43.7 | 43.9 |
| Mean post-bronchodilator $FEV_1$, % of predicted normal | 95.4 | 95.8 |
| Mean pre-study ICS dose, µg | 601 | 607 |

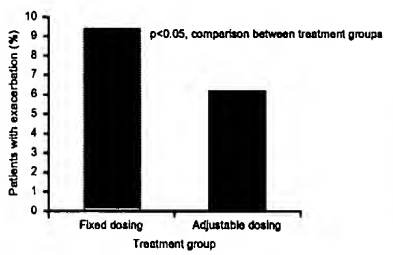
### Run-in

- During the fixed-dose run-in period, most patients previously treated with ICS plus LABA in a single inhaler felt as well or better on Symbicort (subjectively assessed overall treatment evaluation). More patients previously treated with ICS alone or ICS plus LABA in separate inhalers felt better on Symbicort than their previous treatment. PEF improved significantly in patients previously receiving ICS alone for maintenance.

### Efficacy

- Significantly fewer patients in the adjustable dosing group experienced an exacerbation compared with the fixed dosing group (6.19% versus 9.48%, a reduction of 35%, odds ratio 0.653, p<0.05) (Figure 2).

**Figure 2.** Percentage of patients with exacerbation

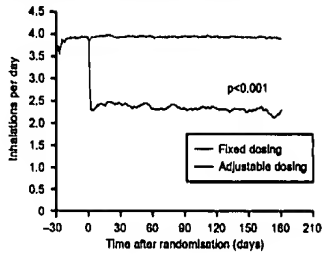



- The mean number of daily inhalations was significantly less in the adjustable dosing group (2.35, compared with 3.95 in the fixed dosing group, a reduction of 40%, p<0.001) (Figure 3).

### Health economics

- Total asthma-related costs were significantly lower in the adjustable dosing group. The mean cost per patient was SEK 3231 (=Euros 349) in the adjustable dosing group, compared with SEK 4124 (=Euros 445) in the fixed dosing group (p<0.001).

**Figure 3.** Daily mean number of Symbicort® inhalations




### Safety

- The incidences of SAEs and DAEs were low and similar in both treatment groups.

## Discussion

These results indicate that the ability to adjust treatment appropriately in response to asthma variation may be an important method of managing the disease and preventing exacerbations. Symbicort may be especially suitable for adjustable dosing as the doses of both budesonide and formoterol in the product fall within their dose response curves.[4,5]

Thus, adjustable treatment with a low maintenance dose may have the potential to reduce the need for oral corticosteroid and treatment in hospital or other healthcare facilities.

## Conclusions

- Symbicort® effectively gains and maintains control of asthma
- Adjustable dosing with Symbicort®:
  - significantly reduces the number of exacerbations compared with fixed-dose treatment, despite using fewer inhalations, and is well tolerated
  - results in a lower total cost compared with fixed-dose treatment

## Clinical Implications

- Symbicort® allows adjustment of maintenance therapy according to the level of patients' symptoms, as recommended in current guidelines.

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AstraZeneca

App. 6

App. 7.

# Tolerability of a High Dose of Budesonide/Formoterol in a Single Inhaler in Patients with Asthma

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Running header: Tolerability of budesonide/formoterol in a single inhaler

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# SUMMARY

This randomised, double blind, double dummy, crossover, placebo-controlled study assessed the acute tolerability of budesonide/formoterol in a single inhaler (Symbicort® Turbuhaler®, AstraZeneca) administered as a high dose.

Fourteen patients with asthma receiving budesonide/formoterol maintenance treatment (two inhalations of 160/4.5 μg twice daily) inhaled 10 additional doses of budesonide/formoterol 1600/45 μg (total daily dose including morning dose of maintenance treatment 1920/54 μg) or formoterol 45 μg (Oxis® Turbuhaler®, AstraZeneca; total daily dose including morning dose of maintenance treatment 54 μg formoterol) or placebo in addition to the morning dose of maintenance treatment on 3 separate study days. Serum potassium, pulse rate, blood pressure and ECG were assessed at regular intervals over a 12-h period following dosing. Blood glucose and plasma lactate were assessed over 3 h following dosing.

Changes in serum potassium, pulse rate, blood pressure, QTc, blood glucose and plasma lactate occurring with budesonide/formoterol, though statistically significantly different from placebo ($P<0.05$), were considered clinically unimportant. No clinically relevant differences were identified between active treatments.

In conclusion, budesonide/formoterol in a single inhaler is well tolerated at high doses such as might be used by patients using budesonide/formoterol for relief of symptoms of asthma.

Word count: 192

Key words: asthma, tolerability, budesonide/formoterol, relief, maintenance

# INTRODUCTION

Patients with asthma are treated with a range of medications often including inhaled glucocorticosteroids and short- and long-acting $\beta_2$-agonists. The efficacy and tolerability profile of these agents is well established and recognised in treatment guidelines.[1] Recently, the inhaled glucocorticosteroid budesonide and formoterol, a $\beta_2$-agonist with a long duration of action, have been formulated as a single inhaler for the treatment of asthma (Symbicort®, AstraZeneca). Budesonide is well established as a safe and effective inhaled anti-inflammatory treatment for asthma and its use is recommended in national and international guidelines.[1] The acute effects of doses of formoterol of up to 90 μg have been assessed in patients with asthma and patients with acute bronchial obstruction, and were found to be clinically unimportant.[2, 3]

Budesonide/formoterol single inhaler is effective in a wide range of doses (one to two inhalations given once or twice daily).[4, 5] Formoterol is unique amongst $\beta_2$-agonists in having a long duration of action and a rapid onset of effect[6, 7] and is suitable for as-needed relief of symptoms. Thus, budesonide/formoterol in a single inhaler could be used for relief of symptoms in the same manner as traditional short-acting $\beta_2$-agonists, as well as for maintenance therapy.[8]

This study was therefore designed to assess the acute tolerability of a high dose of budesonide/formoterol compared with placebo. Since it was anticipated that the acute effects of budesonide/formoterol would reflect the effects observed with formoterol alone, tolerability was assessed using the same variables as measured in studies of the tolerability of formoterol alone.[2, 3] A comparison was also made with

formoterol alone to establish whether the effects of formoterol are changed by concomitant administration of budesonide.

# MATERIALS AND METHODS

## Study subjects

Fourteen outpatients, aged 18–65 years, with a diagnosis of asthma defined according to American Thoracic Society criteria were included in the study. Both male and female patients were included if they were considered to have stable disease and had received regular treatment with budesonide (Pulmicort® Turbuhaler®, AstraZeneca) 400–800 μg daily or equivalent for at least 30 days prior to enrolment in the study. Patients were required to have baseline serum potassium levels within the hospital's reference range (3.5–5.0 mmol/l) and to have given written informed consent. As-needed use of short-acting $\beta_2$-agonists was allowed during the study; other permitted medications included mucolytics and expectorants not containing bronchodilators, and nasal, oral or eyedrop formulations of sodium cromoglycate or nedocromil sodium.

Patients were excluded from the study if they had a history of relevant arrhythmias or heart disease, hypertension or clinically relevant ECG abnormalities including QT prolongations; known or suspected allergy to study treatment; or other significant disease. Patients who had been hospitalised due to exacerbation of asthma in the past 2 months; those treated with oral, parenteral or rectal glucocorticosteroids; patients who had a change in asthma medication within 30 days prior to enrolment; or individuals receiving β-blocker therapy (including

eyedrops) were not enrolled. Pregnancy/lactation, current smoking, and blood donation in the past 3 months also led to exclusion.

Local Ethics Committee approvals were obtained for the study, which was performed in accordance with Good Clinical Practice and the Declaration of Helsinki.

## Study design

This was a randomised, double blind, double dummy, crossover, placebo-controlled study. After enrolment, usual maintenance treatment was discontinued and patients received maintenance treatment for up to 8 weeks with two inhalations of budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca) 160/4.5 μg twice daily (total daily dose 640/18 μg).

There were three tolerability test days during the study: the first was 2–4 weeks after the start of maintenance treatment, and the remaining two days were each 1–4 weeks after the previous test. Administration of a high dose of test treatment (given in a random order) was started immediately after the morning maintenance dose of budesonide/formoterol (between 08.00 and 08.30 on each test day) as follows: single inhaler budesonide/formoterol 1600/45 μg (Symbicort Turbuhaler, AstraZeneca, 160/4.5 μg per inhalation); formoterol 45 μg (Oxis® Turbuhaler®, AstraZeneca 4.5 μg per inhalation); placebo. Test treatment was given as three dose increments over 1 h with 30 min between increments (2 + 4 + 4 inhalations). Thus, total doses on tolerability test days, including the morning dose of

maintenance treatment, were: budesonide/formoterol test day 1920 μg budesonide, 54 μg formoterol; formoterol test day 320 μg budesonide, 54 μg formoterol; placebo test day 320 μg budesonide, 9 μg formoterol.

Serum potassium, pulse rate, blood pressure, 12-lead resting ECG, blood glucose, and plasma lactate were measured at baseline (15 min before inhalation of morning maintenance dose), and at 30, 60, 75, 90, 120 and 180 min after maintenance dosing. Serum potassium, pulse rate, and blood pressure were then assessed every two hours between 4 and 12 hours post-dosing; in addition, ECG was performed 4 and 12 hours after baseline. Measurement of serum potassium and blood glucose was performed according to accredited analyses. The following ranges were considered normal: serum potassium 3.5–5.0 mmol/l, blood glucose 3.3–5.6 mmol/l, plasma lactate 1.0–1.8 mmol/l.

Short-acting $\beta_2$-agonist reliever medication was withheld from 8 h prior to, and during, tolerability testing. Patients fasted for 10 h before attending the clinic on each tolerability test day and until 3 h after the start of dosing when they received a standardised lunch. Subjects rested for 15 minutes before baseline measurements, and avoided strenuous activity or physical exercise during the 36 hours before and 12 hours after visits.

Spontaneously reported adverse events (AEs) and those reported in response to questioning at clinic visits were recorded with information about severity and intensity. An AE was defined as an unintended or unfavourable sign (e.g. abnormal laboratory sign), symptom or disease temporally associated with the use of study medication, whether or not considered causally related to the study medication. A serious AE (SAE) was one that resulted in death, was life threatening, required new

or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, or was a congenital anomaly.

## Statistical methods

For each patient and treatment, the average values for serum potassium concentration, pulse rate, blood pressure, QT-interval, QT-interval corrected for heart rate (QTc, calculated according to Bazett's formula[9]), and blood glucose levels were calculated as the area under the concentration/effect versus time curve divided by the length of the measurement interval. The average and maximal values (or minimal, depending on variable) were analysed using additive analysis of variance models with patients, visit and treatment as fixed factors and baseline value as a covariate. Non-adjusted pairwise comparisons were performed for the three treatments, and the differences were described with means, 95% confidence limits and *P*-values based on these confidence limits.

Differences in the incidence of AEs between groups were analysed by descriptive statistics and qualitative analysis. Tolerability was evaluated from mean and individual data.

This study was primarily descriptive, and on the basis of previous tolerability studies with formoterol, 12 completed patients were judged to provide a good basis for the evaluation of tolerability. In a previous study with formoterol Turbuhaler, the within subject SD in minimum serum potassium over one day was 0.12 mmol/l.[2]

Using a significance level of 5% in the present study, 12 patients would give a detectable difference of 0.15 mmol/l in mean serum potassium with 80% power.

# RESULTS

## Patients

A total of 15 patients were enrolled in the study. One patient failed to meet the inclusion criteria and was withdrawn prior to randomisation. All remaining 14 patients were randomised and completed the study. Baseline demographic data are shown in Table 1.

## Pharmacodynamic assessments

Mean serum potassium levels remained within the normal reference range throughout the test period (Fig. 1), although for all treatments there were individual patients falling outside the reference ranges (budesonide/formoterol, n=8 [lowest 3.0 mmol/l, n=1]; formoterol, n=6 [lowest 3.1 mmol/l, n=2]; placebo, n=3 [lowest 3.3 mmol/l, n=1]). Levels were statistically significantly suppressed following dosing with both active treatments; however, serum potassium also fell with placebo at 4 h after dosing, i.e. after lunch (Table 2).

Mean pulse rate increased after dosing with both active treatments (Fig. 2), and with all three treatments at 4 h after dosing (following lunch). In comparison with placebo and formoterol, budesonide/formoterol treatment had small but statistically

significant effects on average and maximal pulse rate (Table 2). Inter-individual variation was large relative to mean treatment effects.

Both active treatments produced small increases in systolic blood pressure and decreases on diastolic blood pressure. A slight increase in systolic and decrease in blood pressure was seen with placebo at 4 h after dosing.

Overall evaluations of ECGs were normal for all patients at all visits and assessments. QT-interval was slightly prolonged initially after dosing with both active treatments; however, a shortening was observed at 4 h, with both active treatments and placebo. QTc was slightly prolonged with active treatment throughout the 12-h tolerability testing period. Inter-individual differences were large relative to mean treatment effects.

Mean blood glucose levels remained within the normal reference range for all treatments throughout the 3-h assessment period. For all treatments, there were individual patients with values outside the reference range (budesonide/formoterol, n=6 and formoterol, n=3 [both groups highest 6.9 mmol/l, n=1]; placebo, n=1 [5.9 mmol/l]). Blood glucose levels increased during the first 3 h after both active treatments.

Mean plasma lactate levels increased during the first 3 h after both active treatments.

Treatment group comparisons for average and minimal/maximal changes in blood pressure, QT-interval, QTc, blood glucose and plasma lactate are presented in Table 2.

## Adverse events

During tolerability testing, similar numbers of patients reported AEs with each treatment (budesonide/formoterol, n=8; formoterol, n=10; placebo, n=9). The majority of AEs were mild in intensity. No SAEs or discontinuations due to AEs were reported in the study. The most frequently reported events included headache and sore throat, which occurred with similar incidence for each treatment, and $\beta_2$-agonist effects like leg cramps, nausea or tremor, which did not occur after placebo administration (Table 3).

# DISCUSSION

In our study, a high dose of budesonide/formoterol from a single inhaler was well tolerated. As expected, the acute systemic effects observed after tolerability testing with budesonide/formoterol were similar to those seen with formoterol; as discussed below, these were not considered to be clinically relevant.

The acute systemic effects observed in this study were similar to those seen in previous studies of high doses of formoterol and terbutaline. Malolepszy et al[3] reported that inhaled formoterol in delivered doses of up to 90 μg decreased serum potassium by 0.57 mmol/l (mean maximal decrease) and increased heart rate by 3 bpm (mean maximal increase). Similarly, Tötterman et al[2] demonstrated that formoterol was associated with some acute systemic effects. In both of these tolerability studies, inhaled terbutaline 10 mg was associated with significantly more systemic effects than formoterol, as indicated by greater changes in laboratory values for serum potassium, heart rate[2, 3] and cardiac frequency and QTc.[2] The changes observed with formoterol treatment were not considered to be clinically important in either study.

In the present study, changes in serum potassium and pulse rate were seen with high doses of budesonide/formoterol or formoterol alone in the first 3 h after dosing (i.e. during the fasting period). To put these results into context, changes of a similar magnitude also occurred at 4 h with placebo (i.e. after lunch) in the current study, and food effects of a similar extent have been reported in previous studies.[10, 11]

Dose-related systemic effects (pulse, blood pressure, ECG, serum potassium, tremor, plasma glucose) have previously been demonstrated in healthy volunteers on inhalation of four cumulative doses over a 3-h period of a fixed combination of fluticasone/salmeterol (total dose 4000/400 μg), salmeterol alone (400 μg) and placebo.[12] The authors reported similar systemic response between the corticosteroid/$\beta_2$-agonist combination and the $\beta_2$-agonist alone 55 min after dosing. Significant increases in pulse rate of 11 bpm ($p<0.001$) and significant decreases in plasma potassium of 0.27 mmol/l ($p<0.001$) were identified between the combination and placebo. However, in a recent study, the peak bronchodilatory response to fluticasone/salmeterol had not been reached at 3 h,[8] suggesting that the peak systemic effects may not have been observed in the study of Man and co-workers. Also, a study of the systemic effects of salmeterol and formoterol demonstrated that drug-related systemic effects of salmeterol remain at 8 h after dosing.[10] These data support the design of the present study, in which potential acute systemic effects of treatment were monitored for up to 12 hours post-dosing.

This study, the first in patients with asthma to assess the tolerability of a high dose of a glucocorticosteroid and a $\beta_2$-agonist in a single inhaler, demonstrates that budesonide/formoterol is well tolerated without any clinically important effects on serum potassium, pulse rate, systolic and diastolic blood pressure, heart rate, QT-interval, QTc, blood glucose level and plasma lactate level. In conclusion, budesonide/formoterol in a single inhaler is well tolerated at high doses such as might be used by patients using budesonide/formoterol for relief of symptoms of asthma.

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**Table 1** Demographic data

| | **Patients** |
|---|---|
| n | 14 |
| Male/female, n | 6/8 |
| Age, years; mean (range) | 39.6 (21–59) |
| Weight, kg; mean (range) | 80.9 (65–130) |
| Height, cm; mean (range) | 171.3 (158–188) |
| Body mass index, $kg/m^2$; mean (range) | 27.5 (22–38) |
| Smoking history, n (%)† | 5 (35.7) |
| Duration of asthma, years; mean (range) | 21.7 (3–52) |

† Past smokers only, since current smokers were excluded from the study

**Table 2** Comparison of treatment effects between budesonide/formoterol and formoterol or placebo

a) Comparison of average values[a]

| Parameter | Treatment comparison | | |
|---|---|---|---|
| | Mean (95% CI) | | |
| | **Budesonide / formoterol vs placebo** | **Budesonide / formoterol vs formoterol** | **Formoterol vs placebo** |
| Serum potassium (mmol/l) | –0.16* (–0.24, –0.08) | –0.02 (–0.10, 0.07) | –0.14* (–0.23, –0.06) |
| Pulse rate (bpm) | 5.4* (3.1, 7.6) | 3.7* (1.5, 5.9) | 1.7 (–0.5, 3.8) |
| SBP (mmHg) | 2.5* (0.1, 5.0) | –0.2 (–2.7, 2.3) | 2.8* (0.2, 5.3) |
| DBP (mmHg) | –3.3* (–5.6, –0.9) | –1.1 (–3.4, 1.3) | –2.2 (–4.6, 0.2) |
| QT-interval (ms) | 0.4 (–5.6, 6.5) | –5.9 (–12.0,0.2) | 6.3* (0.3,12.4) |
| QTc (ms) | 17.1* (10.5, 23.6) | 2.1 (–4.3, 8.4) | 15.0* (8.4, 21.6) |
| Blood glucose (mmol/l) | 0.44* (0.29, 0.59) | 0.09 (–0.06, 0.23) | 0.35* (0.21, 0.49) |
| Plasma lactate (mmol/l) | 0.19* (0.11, 0.28) | –0.08 (–0.18, 0.02) | 0.28* (0.18, 0.38) |

[a] Treatment differences shown for the average values recorded over a 12-h period following dosing except for blood glucose and plasma lactate which were measured over a 3-h period

* $P<0.05$

b) Comparison of maximal values after dose intake[b]

| Parameter | Treatment comparison<br>Mean (95% CI) | | |
|---|---|---|---|
| | **Budesonide / formoterol vs placebo** | **Budesonide / formoterol vs formoterol** | **Formoterol vs placebo** |
| Serum potassium (mmol/l) | –0.21* (–0.34, –0.08) | –0.07 (–0.20, 0.06) | –0.14* (–0.27, –0.01) |
| Pulse rate (bpm) | 7.6* (4.8, 10.3) | 5.5* (2.7, 8.2) | 2.1 (–0.6, 4.8) |
| SBP (mmHg) | 3.2 (–0.5, 6.9) | –0.2 (–3.9, 3.5) | 3.4 (–0.2, 7.1) |
| DBP (mmHg) | –5.2* (–8.8, –1.6) | –2.3 (–5.9, 1.2) | –2.9 (–6.5, 0.7) |
| QT-interval (ms) | 10.4* (3.5,17.4) | –3.0 (–10, 4.0) | 13.4* (6.4, 20.5) |
| QTc (ms) | 26.5* (18.1, 34.8) | 4.8 (–3.4, 13.0) | 21.7* (13.2, 30.1) |
| Blood glucose (mmol/l) | 0.85* (0.59, 1.11) | 0.28* (0.03, 0.53) | 0.57* (0.33, 0.81) |
| Plasma lactate (mmol/l) | 0.34* (0.13, 0.54) | –0.18 (–0.42, 0.06) | 0.52* (0.28, 0.75) |

[b] Treatment differences shown for the maximal values except for diastolic blood pressure and serum potassium which are minimal values. Maximal/minimal values were recorded over a 12-h period following dosing except for blood glucose and plasma lactate which were measured over a 3-h period

* $P<0.05$

**Table 3** Adverse events reported by more than one patient on tolerability test days

| Adverse event (number of patients) | Budesonide / formoterol (n=14) | Formoterol (n=14) | Placebo (n=14) |
|---|---|---|---|
| Headache | 6 | 7 | 5 |
| Pharyngitis | 2 | 0 | 2 |
| Cramps | 1 | 3 | 0 |
| Nausea | 3 | 0 | 0 |
| Tremor | 1 | 1 | 0 |

# FIGURE LEGENDS

Fig. 1 Mean serum potassium levels on tolerability test day.

Fig. 2 Mean pulse rate on tolerability test day.

Fig. 1

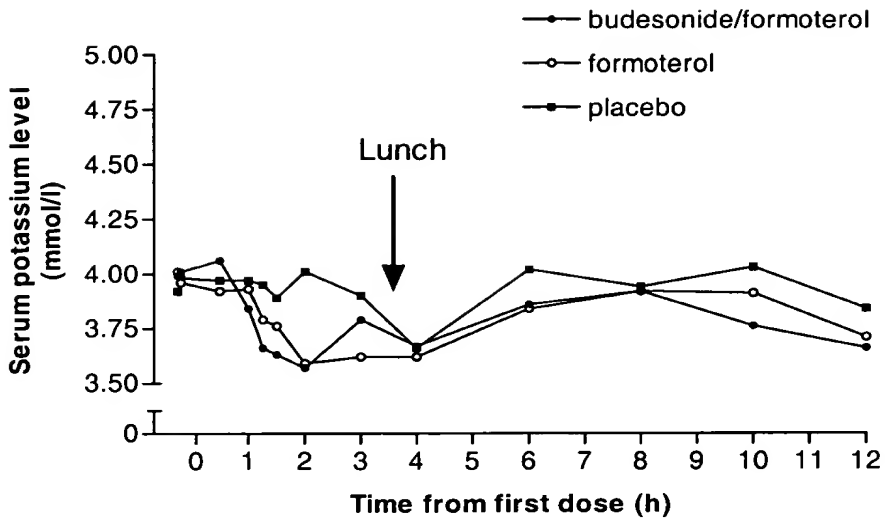
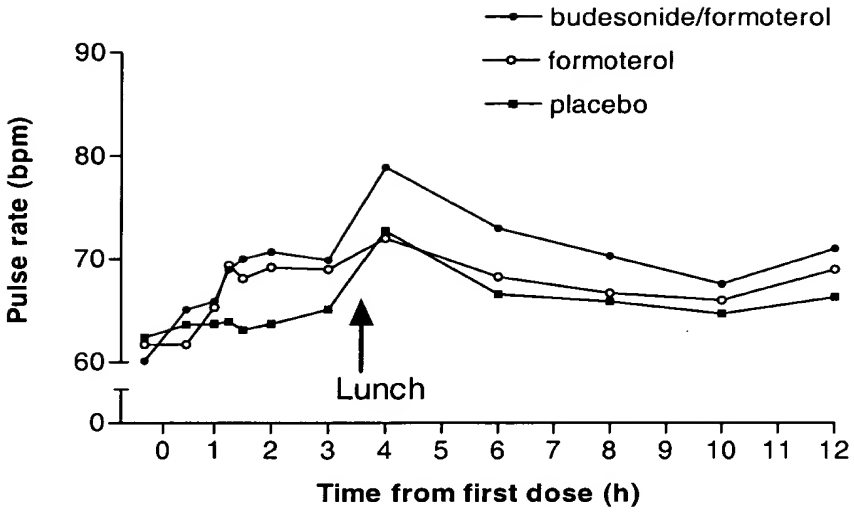

budesonide/formoterol
formoterol
placebo
Lunch
Serum potassium level (mmol/l)
5.00
4.75
4.50
4.25
4.00
3.75
3.50
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time from first dose (h)

Fig. 2


budesonide/formoterol
formoterol
placebo
Pulse rate (bpm)
90
80
70
60
0
Lunch
0 1 2 3 4 5 6 7 8 9 10 11 12
Time from first dose (h)